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THE ACTIVITY OF WILD AMERICAN DIGITALIS.

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The necessity for the utilization of every available source in the collection of crude material for the preparation of botanic drugs has perhaps never been so urgent as at the present time. For obvious reasons the price of crude drugs has advanced greatly within the past few years, among these drugs being digitalis. Under normal conditions the greater part of the supply of digitalis came from Germany and Austria, and since these sources of supply have been removed the available stock has been greatly diminished. At the outbreak of the European war, when a shortage in the supply of crude botanic drugs was first felt, many original articles and editorials appeared in the various drug and pharmaceutical journals for the purpose of awakening an interest in drug-plant culture, suggesting this means as a remedy for the shortage. Although interest in the growing of drug plants is increasing constantly, there are so many difficulties in the way of their successful production on a commercial scale that the cultivation of digitalis for example has not been extensive enough to fill the present need. The maximum quotation on ordinary digitalis leaves, as given in the Druggists Circular for November, 1913, was 30 cents per pound, while for Allen's powdered leaves the maximum quotation was $1 per pound. The same drug journal for November, 1916, gave maximum quotations of 80 cents for the former and $2 for the latter, although drug cultivation was encouraged during these years.

Recently Wilbert[1] called attention to a hitherto neglected source for obtaining digitalis, namely, in the collection of the wild-growing plant which has escaped from cultivation and has now become a "weed" in various sections of the United States. Fortunately the digitalis which is now found growing wild in great abundance in California, Oregon, Washington, and to some extent in West Virginia is the Pharmacopœial variety, *Digitalis purpurea*. However, if the wild-growing American digitalis is to be of commercial importance for the manufacture of the official preparations of digitalis, its activity must be at least as great as that required by the Pharmacopœia. This question, therefore, was investigated by examining the activity of four samples of wild-growing leaves which were collected in the State of Oregon during the season of 1916 and one sample of wild-growing leaves obtained from the State of Washington during the same season. For the purpose of comparison examination was also made of cultivated digitalis leaves (*Digitalis purpurea*) which were grown in the State of Washington during the season of 1916. Inclusion was also made of two samples of cultivated digitalis leaves of the season of 1914 which were examined shortly after their harvest, one sample being grown in Wisconsin, the other in Ohio. Tinctures were made according to the United States Pharmacopœia method from all the samples and their activity was determined physiologically by the method originally adopted by the Hygienic Laboratory, which is now the method recommended by the Pharmacopœia, namely, the one-hour frog method. The Oregon digitalis was obtained through the kindness of Mr. I. E. Gaston, a student in the medical department of the University of Oregon.

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[1] "The Source and Supply of Medicines with Special Reference to the Interference Caused by the European War," Martin I. Wilbert, United States Public Health Reports, Oct. 9, 1914, pp. 2715-2718.

A sample of the undried Oregon leaves was submitted for identification to the writer, who submitted them to Dr. W. W. Stockberger, of the United States Department of Agriculture, and by whom they were identified as *Digitalis purpurea.* All of the Oregon digitalis was collected near Astoria, Oreg. Sample 1 consisted of leaves gathered from first-year plants about six weeks after the flowering time for digitalis. They were rather dark green in color, the hairs being practically free from soil. They were well dried, crushing easily when rolled between the fingers. Sample 2 consisted of leaves gathered from second-year or older plants, about six weeks after flowering time. They were light green in color, well dried and free from soil. Sample 3 consisted of leaves collected from flowering plants (second-year or older plants); while sample 4 consisted of leaves from plants which had partially dried on the stalk and were yellowish-green in color.

According to Mr. Gaston all the samples which he collected were found growing upon soil containing considerable clay. He states that they will thrive on practically any soil that will absorb moisture readily. The largest and best leaves were from plants which grew on moist ground where the plants were shaded about half the day. Too much shade seemed to prevent their proper development, while long exposure to the sun caused the leaves to turn yellowish. All of the samples were air-dried immediately after the leaves were collected, except sample 4, which was dried on the stalk for the most part. The procedure used for samples 1, 2, and 3 was as follows: The freshly gathered leaves were spread out in thin layers on floors over which the air could circulate freely, and stirred frequently, at least every other day. They will retain their green color if dried in this way and if stirred frequently do not mold. About three weeks were required to dry them thoroughly, inasmuch as rainy weather was present during about half of the time.

Samples 5 and 6 were collected and dried by Prof. A. W. Linton, of the University of Washington College of Pharmacy. Sample 5 consisted of leaves from plants growing wild near Seattle, Wash., being collected in August while the plants were in blossom. They were air-dried, being very dry and brittle, and were tinged with yellow. Sample 6 consisted of leaves from cultivated plants of second-year growth, which were obtained from the drug garden of the College of Pharmacy, University of Washington. They were collected in November, 1916, and are the second growth of leaves for the season. The air-dried leaves were green and, like sample 5, were very brittle. Sample 7 consisted of leaves from first-year cultivated Wisconsin digitalis collected in 1914, before flowering had occurred. The dried leaves were green and were free from soil. They were supplied by Prof. Edward Kremers, of the University of Wisconsin, being raised on the university drug farm. Sample 8 consisted of leaves from first-year cultivated digitalis which was grown in Cincinnati, Ohio. It was collected in November and was supplied by Prof. John Uri Lloyd. It was yellowish green when dried. The method in which the last two samples were dried is unknown. As previously stated, these samples were all examined by the one-hour frog method. Their value by this method together with a short description of the sample will be given in the table below. The doses of the tinctures given in the table represent mils per gram of body weight.

Sample No.	Description of sample.	Lethal dose of ouabain.	Lethal dose of standard tincture digitalis.	Lethal dose of sample tincture.	Corrected lethal dose of sample tincture.
1	Oregon, wild, 1916	0.00000055	0.0066	0.004	0.0036
2	do	.00000055	.0066	.005	.0045
3	do	.00000045	.0054	.004	.0044
4	do	.00000045	.0054	.003	.0033
5	Washington, wild, 1916	.00000045	.0054	.011	.0121
6	Washington, cultivated, 1916	.00000045	.0054	.007	.0077
7	Wisconsin, cultivated, 1914			.003	
8	Ohio, cultivated, 1914			.006	

Samples 1 and 2 were assayed on a lot of frogs received in October; samples 3 to 6, inclusive, were assayed on a lot of frogs received one month later. All of the samples were assayed on *Rana pipiens*, which were all obtained from the same dealer. Since the frogs used in the standardization of samples 7 and 8 were not standardized against ouabain, no comparative figures can be computed for these samples. It may be stated, however, that the resistance of the frogs usually lies within a range of 10 per cent.

The United States Pharmacopœia IX requires that by the above method 0.006 mil of the tincture of digitalis per gram of frog weight shall be necessary to stop the heart of the frog in one hour. From the above table it is seen that all of the samples of wild Oregon digitalis were stronger than the pharmacopœial standard.

While this investigation has shown that of the tinctures made from wild-growing digitalis, the Oregon samples were several times stronger than that grown in Washington, we should not conclude that wild Oregon digitalis is generally more active than wild Washington digitalis. Further examination of the latter would be necessary to determine this point definitely. Inasmuch as the tincture made from cultivated Washington digitalis is weaker than the tinctures made from any of the Oregon samples, it is likely that the correct explanation of the decreased activity of Washington digitalis is to be sought in sources other than in the manner of growing.

Table 1 also shows that cultivated digitalis is not necessarily less active than wild digitalis and that individual samples may be as active as the most active sample made from wild leaves.

What was especially surprising to the writer was to find that sample 4, which was made from leaves that had partially dried on the stalk, was the most active of the Oregon samples. As stated before, these leaves were yellowish-green in color and would ordinarily be regarded as leaves of poor quality.

Again, when we consider the samples made from wild Oregon leaves we find that the time of collection of the leaves with reference to the flowering time of the plants has little to do with their activity, since sample 1, which was collected from first-year plants, was a little more active than sample 3, which was collected from flowering plants.

The fact that all of these samples were air-dried is of especial significance, inasmuch as almost every writer on the subject of digitalis activity considers that special methods of drying are necessary to secure a good product. Newcomb[1] prefers the use of drying ovens and artificial heat maintained at 100° C. for eight-hour periods on three successive days. This method is considered by him to destroy the ferments contained in the leaves without injury to the active principles; besides, it fixes the green color which is a valuable commercial asset.

From the above investigation we may conclude that the wild digitalis which is found in the Northwestern States may be utilized as a source of supply for making the various official preparations of digitalis, and that by using ordinary methods in handling and preparing the leaves we may secure a highly active product, which compares favorably with the activity of cultivated leaves grown under more favorable conditions.

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[1] "Digitalis, Its Cultivation, Collection, and Preparation"; Edwin L. Newcomb, Am. J. Pharm., 1912, v. 84, p. 201.